

Premio “Cinzia Chiappe” Ed. 2023

Tommaso Fantoni

Titolo Tesi di Dottorato

Green approach to Palladium Cross-Coupling reactions and development of new methodologies based on highly abundant metals

Corso di Dottorato

CHIMICA ORGANICA, Ciclo XXXV

Tutor

Prof. Walter Cabri

Alma Mater Studiorum – Università di Bologna, Dipartimento di Chimica “Giacomo Ciamician”

Sintesi della Tesi

Transition metal catalyzed cross-coupling reactions represent among the most versatile and useful tools in organic synthesis for the carbon-carbon (C-C) bond formation and have a prominent role in both the academic and pharmaceutical segments. Among them, palladium catalyzed cross-coupling reactions are currently the most versatile. However, considering the increasing growth in the price of palladium during the last years, attempts to reduce its loading and to perform its recycling and recovering represent an inescapable necessity, especially if the final outlook is to apply reactions at industrial level. Our research group proposed a translation of the twelve green chemistry principles [1] into practical suggestions (Figure 1) to stimulate the development of cost-effective and sustainable catalytic processes for the synthesis of active pharmaceutical ingredients (API).

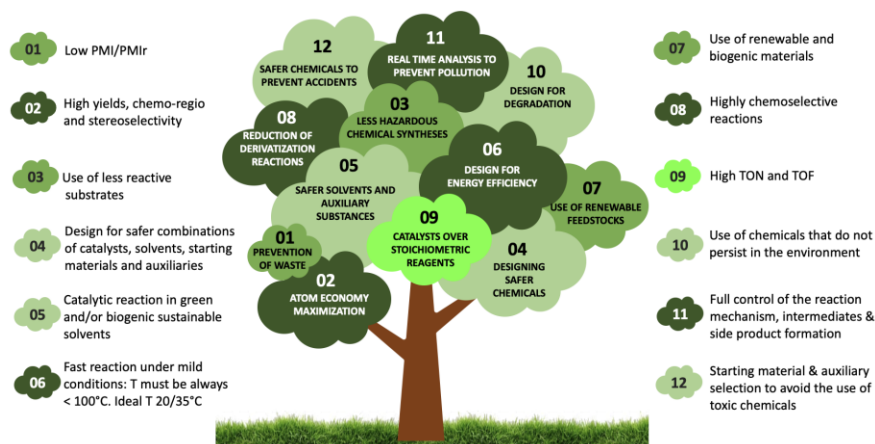


Figure 1: Translation guide of the Twelve Principle of Green Chemistry for Cross-Coupling reactions

An efficient and sustainable protocol for the Heck-Cassar-Sonogashira (HCS) and the Suzuki-Miyaura (SM) cross-coupling reactions was developed using 1-(2-Hydroxyethyl)-2-pyrrolidone (HEP)/H₂O as green mixture and sulfonated phosphine ligands. The optimized condition allowed to recycle and recover the catalyst, always guaranteeing high yields and fast conversion under mild conditions, with aryl iodides, bromides, triflates and chlorides [2, 3]. No catalyst leakage or metal contamination of the final product were observed during the HCS and SM reactions, respecting the very low limits for metal impurities in medicines established by the International Conference of Harmonization Guidelines Q3D (ICH Q3D). In addition, a deep understanding of the reaction mechanism is very important if the final target is to develop efficient protocols that can be applied at industrial level. Experimental and theoretical studies pointed out the presence of two catalytic cycles depending on the counterion, shedding light on the role of base in catalyst reduction and acetylene coordination in the HCS coupling. Finally, the development of a cross-coupling reaction to form aryldifluoronitriles in the presence of copper was discussed, highlighting the importance of inserting fluorine atoms within biological structures and the use of readily available metals such as copper as an alternative to palladium.

Riferimenti

1. Fantoni et al, *Catal.Today*, **2022**, 397, 265-271
2. Fantoni et al. *ChemSusChem*, **2021**, 14, 2591–2600
3. Ferrazzano et al. *Org.Lett*, **2020**, 22, 3969–3973